

## AMENDMENTS

### **In the claims:**

Please add claim 9.

1. (previously presented)) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. (previously presented) An isolated nucleic acid molecule comprising a nucleotide sequence that:

- (a) encodes the amino acid sequence shown in SEQ ID NO:2; and
- (b) hybridizes under highly stringent conditions to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3.(original) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO: 2.

4.(original) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO: 8.

5.(previously presented) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 3.

6.(previously presented) A host cell comprising the recombinant expression vector of claim 5.

7. (previously presented) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 4.

8.(previously presented) A host cell comprising the recombinant expression vector of claim 7.

9.(new) The nucleic acid molecule of claim 4 wherein the nucleotide sequence is that of SEQ ID NO: 7.

## **RESPONSE**

### **I. Status of the Claims**

Dependent claim 9 has been added to better claim the present invention. Claims 1-9 are therefore pending in the present case.

### **II. Support for the Amended Claims**

New claim 9 has been added to better claim the present invention. New claim 9 finds support throughout the specification as originally filed with particular support for hybridization being found in original claim 4 on which it depends.

As new claim 9 is fully supported by the specification, sequence listing and claims as originally filed, it does not constitute new matter. Entry is therefore respectfully requested.

### **III. Rejection of Claims Under 35 U.S.C. § 101**

The Action rejects the claims under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants strongly disagree, and continue their traverse by summarizing some previously presented arguments and elaborating on others the role of the protein encoded by the sequences of the present invention in human disorders.

Applicants respectfully submit that the sequences of the present invention encode a novel human CD20 antigen-like membrane protein, that plays a role in connective tissue disorders (specification at page 12, line 9) and is involved in the regulation of the levels of Natural Killer (NK) cells.

The Final Action states that Applicants have failed to establish biological functions or any physiological significance of the molecules of the present invention (Action on page 3) and have provided no disclosure with regard to the relationship between the sequences of the present invention and any disease or disorder (Action on page 6).

Applicants respectfully submit that such is not a requirement. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful

for any particular purpose (i.e., it has a “specific and substantial utility”) and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

However, even though it is not required, Applicants respectfully submit additional evidence regarding the role of NK cells in connective tissue diseases and disorders. The evidence and discussion that follows was not presented previously as it was thought that the role of NK cells in connective tissue diseases and disorders was well-known and therefore required no direct evidence. Apparently this is not the case given the present situation.

Systemic Sclerosis is a chronic inflammatory connective-tissue disorder characterized by fibrosis of skin and viscera in humans. Those of skill in the art recognized the role of NK cells in the pathophysiology of such connective tissue disorders prior to Applicants’ filing (see, for example, Wanchu, *et al.*, Lack of natural killer cell augmentation in vitro by human interferon gamma in a subset of patients with systemic sclerosis, *Pathobiology*, 63(5):288-92, 1995: **Exhibit A**). The relationship between NK cells and, for example, systemic sclerosis has been verified by those of skill in the art, see Ercole *et al.*, 2003 (Analysis of lymphocyte subpopulations in systemic sclerosis, *J Investig Allergol Clin Immunol.* **13**(2):87-93: **Exhibit B**), who found that patients with diffuse and late-stage disease had smaller percentages of NK cells. Thus, clearly those of skill in the art recognize the role of NK cells in connective tissue disorders such as systemic sclerosis.

Applicants previously described in their earlier Responses (paper nos. 10, 13 and 20), various forms of evidence supporting the real world utility of this human CD20 antigen-like membrane protein encoded by the sequences of the present invention and particularly in paper no. 20, Applicants’ findings involving the analysis of transgenic “knockout” mice (which were described in the specification, at least on page 2, lines 17-20), in which the function of the gene encoding the sequences of the present invention were disrupted in gene trapped murine embryonic stem cells.

These Knockout mice, that were prepared as described in the specification, were subject to a medical work-up using an integrated suite of medical diagnostic procedures designed to assess the function of the major organ systems in a mammalian subject. Disruption of the mouse homologue of the gene of the present invention and thus elimination of the protein it encodes, resulted in an increase, approximately doubling the number of natural killer (NK) cells that were detected in the blood of animals in which this gene activity had been disrupted. This clearly provides evidence that the protein

encoded by the sequences of the present invention play a role in connective tissue disorders, as described in the specification as filed and has a biological function. It plays a role in the regulation of NK cell levels. And clearly, as evidenced above, those of skill in the art would recognize the role of NK cells in connective tissue disorders such as systemic sclerosis. Therefore, as stated in the specification as filed the molecules of the present invention as well as agonists or antagonists directed at them can be used to diagnose and treat disorders that involve altered NK cell numbers such as, for example as described in the specification as filed connective tissue disorders like systemic sclerosis. Thus clearly, as validated drug targets for diseases involving altered NK cell levels, such as connective tissue disorders like systemic sclerosis, the molecules of the present invention also have real world substantial and specific utility. Those of skill in the art would clearly recognize the utility of the present invention in addressing connective tissue disorders as well as be enabled to make and use the present invention without undue experimentation. Thus, the present invention clearly has credible and well established utility. In light of the evidence presented above and in previous responses, Applicants respectfully submit that the present invention is in full compliance with the provisions of 35 U.S.C. § 101, and respectfully request that the rejection be withdrawn.

Of note, the Examiner is correct in pointing out that Applicants incorrectly and unintentionally identified the amino acid sequence of SEQ ID NO:2 of the present invention as identical to Accession No. Q9H3V2 (amino acid sequence comparison provided previously as Exhibit C in paper no. 20) which third party scientists *wholly unaffiliated with Applicants* have annotated as encoding “Membrane-spanning 4-domains subfamily A member 5 (MS4A5) (testis-expressed transmembrane 4 protein) (CD20 antigen -like 2)”. Furthermore, the amino acid sequence of SEQ ID NO:2 is identical to the CD20 containing portions of several MS4A5 proteins (for example accession no NM\_023945). SEQ ID NO:2 clearly represents a variant of Accession No. Q9H3V2. Supporting this conclusion is the description in the specification that the sequences of the present invention, a variant of MS4A5, were also found to be expressed in human testis.

In addition to the utility presented above, additional utilities for the sequences of the present invention include assessing temporal and tissue specific gene expression patterns (specification at page 6, line 3), particularly using a high throughput “chip” format (specification at page 5, line 8 through page 7). The Final Action, however, discounts Applicants’ assertions regarding the use of the presently

claimed polynucleotides on DNA chips, based on the position that such a use would allegedly be generic and because the sequences of the present invention have not been associated with a human disease or disorder.

As set forth in Applicants' First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described sequences which encodes a human CD20 antigen-like membrane protein that regulates NK cell levels which are as described in the specification as filed associated with connective tissue disorders have utility.

The Final Action suggests that while DNA chip technology itself has utility, the present sequences, which describe specifically the human CD20 antigen-like membrane protein do not. The Action argues that something that is absolutely essential to and greatly enhances the value of a patented technology has no utility itself. The sequences of the present invention, which encode variants of the human CD20 antigen-like membrane protein and which have a characterized tissue expression pattern provide specific markers for the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease, specifically connective tissue diseases such as systemic sclerosis. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

The Examiner is further requested to consider that, given the huge expense of the drug discovery process, even negative information obtained using these specific markers of expression of human CD20 antigen-like membrane protein with a characterized tissue expression pattern provide very specific markers for the human genome and have great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of DNA gene chips, such as the presently claimed sequences encoding a human CD20 antigen-like membrane protein that regulates NK

cell levels must in themselves be useful. Moreover, the presently described human CD20 antigen-like membrane protein provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences, which encode a protein involved in human connective tissue disorders via the regulation of NK cell levels provides an exquisitely specific utility for analyzing gene expression.

Additionally, as previously stated, only a small percentage of the genome (2-4%) actually encodes exons, which in turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. This further discounts the Examiner's position that such uses are "generic". The present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome (specification at page 10, line 18), for example mapping the protein encoding regions as described in the specification and evidenced below. Clearly, the present polynucleotide sequences provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding a human CD20 antigen-like membrane protein whose expression affects NK cell levels, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence supporting the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra* at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

Presented previously as Exhibit E in Applicants' Response (paper no. 20) was evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information that was provided. This evidence resulted from overlaying the SEQ ID NO:1 of the present invention and the identified human genomic sequence. By doing this, one is able to identify the portions of the genome that encode the present invention. If these regions of the genome are non-contiguous, this is indicative of individual exons. The results of such an analysis indicates that the sequence of the present invention is encoded by 5 exons spread non-contiguously along a region of human chromosome 11, which is contained within Accession no. AP001034.5 in the BAC clone RP11-729B4. Thus clearly one would not simply be able to identify the 5 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were. Additionally, it should be noted that the human MS4A5 gene has since been mapped to the same region of human chromosome 11 (at approximately 11q12). This further supports Applicant's position that the sequences of the present invention encodes a variant of human MS4A5 is evidence supporting

Applicants earlier assertions of the specific utility of the sequences of the present invention in localizing the specific region of human chromosome 14 and identification of functionally active intron/exon splice junctions.

In summary, the specification of the present invention describes, as was asserted in the application, sequences that encode a human CD20 antigen-like membrane protein, specifically that known to the art as MS4A5. In the specification Applicants asserted that the sequences of the present invention had utility in, among other things, the diagnosis and prognosis of human connective tissue disorders. Applicants have described evidence obtained using knockout mice that were constructed as described in the specification as filed, that clearly demonstrate that Applicants' assertion regarding the role of the protein encoded by the sequences of the present invention in connective tissue disorders was credible and that those of skill in the art would have clearly recognized that assertion as credible. Further, the sequences of the present invention, that encode human CD20 antigen-like membrane protein variants, have particular utility in DNA chip analysis due to their association with human connective tissue disorders as well as other NK cell mediated disorders. In addition, as described in the specification, these sequences were used to map that region of human chromosome 11 which encodes this human CD20 antigen-like membrane protein. This utility has been evidenced by Applicants' submission as well as by the work of other. Therefore, Applicants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of the pending claims under 35 U.S.C. § 101 should be withdrawn.

#### **V. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph**

The Action also rejects the pending claims under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as the sequences of the present invention have been shown to have a specific, substantial, credible and well established utility, as detailed in section IV above, Applicants therefore respectfully request that the rejection of claims under 35 U.S.C. § 112, first paragraph, be withdrawn.